IECM - Immuno-endocrinologie cellulaire et moléculaire

Rapport Hcéres

agence d'évaluation de la recherche
et de l'enseignement supérieur

Section des Unités de recherche

AERES report on the research unit

Immuno-endocrinologie cellulaire et moléculaire

From the

ONIRIS

INRA

Université de Nantes

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

March 2011

Research Unit

Name of the research unit: Cellular and Molecular Immuno-Endocrinology Unit / Immuno-endocrinologie cellulaire et moléculaire

Requested label: UMR_MA ONIRIS/University, USC INRA

N° in the case of renewal :

Name of the director: M. Jean-Marie BACH

Members of the review committee

Committee chairman:

M. Peter VAN ENDERT, Université Paris Descartes, Paris

Other committee members:

M. Jerome ALEXANDRE, Université Paris Descartes, Paris

Ms Nathalie CHAPUT, IGR, Villejuif

Ms Clothilde THERY, Institut Curie, Paris

M. Antoine TOUBERT, Université Paris Diderot, Paris

Ms Catherine RONIN, Université de Provence (CSS INRA)

Observers

AERES scientific advisor

Ms Ana-Maria LENNON-DUMESNIL

University, School and Research Organization representative

M. Alain CHAUVIN, ONIRIS and Université de Nantes

M. Christian DUCROT, INRA

Report

1 • Introduction

- **Date and execution of the visit:**

The site visit took place on February 15, 2011 between 3 pm and 6 pm. The unit was presented in a room of a biomedical center of the University hospital Nantes, thus the premises of the unit were not inspected by the commission. The presentation was organized in an initial presentation of the history, environment, structure and project of the unit by its director, followed by presentations of the two main projects (type 1 diabetes and autonomous nervous system, miRNAs in beta cells and type 1 diabetes. After a discussion, the jury split in three parts and met permanent staff scientists, technicians and students in parallel. The visit ended with a short closed discussion among jury members.

- **History and geographical localization of the research unit, and brief presentation of its field and scientific activities**

This unit is the successor to a research unit founded in 1979 at the Faculty of Medicine of the University of Nantes. The unit obtained co-accreditation by INRA in 1992 and become – after having moved to the Veterinary College of Nantes in 1994 – an UMR INRA/University/Veterinary College (UMR_A) in 1998. Recently, the Veterinary College merged to an agricultural engineering school to become the ONIRIS entity. The principal activity of the unit has always been related to diagnostic and therapeutic approaches for type 1 diabetes, including an interest in strategies for beta cell replacement. Next to this, the unit has had a strong and consistent implication in teaching for students of the Veterinary school. Following previous reviews organized by INRA in 2005 and 2007, the unit undertook a restructuring and refocusing in 2006, under the directorship of its present director. In the application presented, the unit undertakes an additional round of refocusing, shedding on the occasion the majority of its researchers with teaching duties while retaining most technical staff and all other researchers. The unit also will change affiliation and be affiliated as UMR_MA with the University of Nantes and the recent created ONIRIS entity (formed by a merger of the Veterinary school with an agricultural engineering school) associated with an USC INRA.

- **Management team**

The unit is directed by M. Jean-Marie BACH (ONIRIS). Unit governance involves a number of committees in charge of quality control, hygiene and security, scientific animation, rodent facilities, metrology, and an immunomonitoring platform. An executive committee (5 members) and a unit council (all unit members) decide on various matters.

- **Staff members**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	7	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	8.6	6.35
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0.5	0.5
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	1
N7: Number of staff members with a HDR or a similar grade	5	3

2 • Overall appreciation on the research unit

- **Summary :**

Globally this is a well-managed unit using efficient local networking that continues a thematic and personnel restructuring started 5 years ago. The results obtained during the previous mandate were of heterogeneous quality. Projects related to CD8+ T cell epitope discovery in type 1 diabetes showed a good productivity resulting in publications with good impact and citation rates, while 3 other projects produced limited results of low impact. “Incubation” of a now independent group dedicated to establishing pet models for human cancer is an additional notable result. The project lists three lines of research two of which appear well structured while the third is still “under construction” and lacks adequate funding and staff to be arranged in collaboration with the local IHU initiative. The first project aims to produce tolerogenic antigen-presenting cels using ß2-adrenergic stimulants. While some data suggesting an effect of these reagents on Antigen Presenting Cells (APCs) are presented, data showing that these reagents protect from diabetes are not yet available. It will be important to focus on obtaining this evidence to confirm the relevance of this potentially important project as a therapeutic approach for type 1 diabetes. The second project will examine micro RNAs as immunostimulatory and gene-silencing reagents in diabetes. This project is supported by some interesting preliminary data and has the potential to develop into a cutting-edge program. The programmed experimentation is highly ambitious and represents significant risks with respect to competition, technical challenges, funding, and staff expertise.

- **Strengths and opportunities**

- Efficient unit management ;

- Expertise in research using the Non Obese Diabetes (NOD) model and lymphocytes from type 1 diabetes patients ;

- High potential specifically of project 2 ;

- Adaptation of project 3 to specific environment and specifc expertise ;

- Interesting local collboration in project 3.

- **Weaknesses and threats**

- Technical and scientific challenges for staff due to recent re-orientiation ;

- Limited availablity of most scientists due to teaching duties, with imbalance scientists vs. technicians and engineers ;

- Dearth of post-docs and tenured researchers without teaching duties ;

- Uncertainty with respect to clinical relevance of project 1 ;

- Strong competition in project 2 ;

- Uncertainty with respect to manpower and funding for project 3 ;

- Globally limited success in fund raising.

- **Recommendations to the head of the research unit**

- In project 1, focus on rapidly confirming therapeutic and/or prophylactic efficacy of ß2-stimulants in the NOD model ;

- Seek collaboration with teams with confirmed expertise relevant for project 2, which could also be helpful for fundraising ;

- Benefit from specific strengths, opportunities and environment in developing project 3 ;

- Enhance efforts to obtain funding and recruit postdocs and tenured researchers without teaching duties.

- **Production results**

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	6
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	1
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	0.875
A4: Number of HDR granted during the past 4 years	2
A5: Number of PhD granted during the past 4 years	6

3 • Specific comments

- **Appreciation on the results**

During the last 4 years, unit researchers have been involved in 5 projects. The results with the greatest impact were obtained in project 1, autoreactive CD8+ T cells and their controls. Efforts to discover CD8+ T cell epitopes were quite successful and allowed for publication of several papers with good impact and citation rates. In addition, there is an ongoing project in which CD8+ cells from pancreas graft recipients are monitored for phenotype and function, but few or no results seem to be available yet. Moreover, inital results concerning miRNAs were obtained in this context (see below). A second project dealt with reagents rendering dendritic cells tolerogenic. A number of results were obtained with heme oxygenase 1, however this research was apparently abandoned for reasons that are not spelled out, and the investigators switched to using ß2-adrenergic stimulation for DC « conditioning ». Two more long-standing projects related to myeloid-derived suppressors and to transduction of hepatocytes with the aim to generate insulin-producing cells were continued but seem to have produced little remarkable results in the period. A fifth project, thematically set apart from all other projects, had the aim to set up pet animal models for human mammary cancers and B cell lymphomas. The unit is obviously well placed to develop this project which has been able to attract good funding. Having been « incubated » by the unit for several years, the pet cancer project carried by several unit researchers has given rise to an independent group that will not be part of the unit in the future. In summary, the unit has studied a large number of projects, however the main impact and originality of the research concerned discovery of epitopes derived from type 1-diabetes autoantigens, while other projects were either little productive or produced preliminary results that are the foundation for the project (see below). Incubation of a promising pet cancer group is another significant result.

Unit scientists have published a total of 13 publications in the first or last author positions over the last four years. Another 10 publications are co-authored. Consistent with what is said above, the highest (good) impact was obtained for epitope discovery studies, while other publications tended to have low impact (less than 5 citations). All but one of the researchers are publishing according to AERES criteria. Unit scientists made 11 oral or poster presentations at international meetings and some more at national ones. According to the application, publication activity has increased by 40% relative to the previous 4-year period. Six students defended their thesis during the period.

The unit is very well integrated in a local network of partnerships. These include the entity produced by the fusion of the veterinary and engineering schools (ONIRIS), the University of Nantes and three local INSERM units. The unit is also part of a local IHU (Institut Hospitalo-Universitaire) project focusing on transplantation in which it will focus on development of pigs as organ donors.

- **Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners**

Units scientists did not receive awards in the period concerned. There were no invitations to speak at international conferences. One unit member was invited to chair a session at the EASD meeting 2005 in Athens.

The unit has not been able to recruit high level scientists or postdocs in the period under consideration. One energetic young scientist with teaching duties employed by ONIRIS was recruited to the unit. This scientist will take a leading role in one of the two principal projects in the future, making this a successful recruitment.

Unit leaders have been moderately successful in fund raising over the last years. Next to recurrent lump sum fuding of 70 k€ per year, the unit has obtained a total of about 500 k€, of which 200 k€ were given from industry, University and INRA for the pet cancer project. However, the unit is fairly well equiped due to successful fund raising from regional sources. For example, a FACS Aria state-of-the-art cytometer has been purchased.

The unit coordinates a regional network for recruitment of type 1-diabetes patients and also recruits and monitors recipients of pancreas grafts. Its participation in the local IHU project implies participation in an emerging European network dedicated to developing pigs as organ donors (« European pig for medical use network »). However, this network apparently has not yet obtained funding. Collaborations with European groups in Louvain (Belgium) and Padua (Italy) are part of this network under construction.

The unit runs an immunomonitoring platform which is offered as a service to local academic and industry partners.

- **Appreciation on the strategy, management and life of the research unit**

This unit appears to be very well managed. The unit disposes of a variety of committees ensuring consensual planning and scientific development that involves and motivates all members. Critical tasks and reglementation requirements are taken care of by assigned members. Hygiene and safety is taken serious and a folder with rules and procedures is available to unit members. Regular scientific meetings are held. Separate discussions of jury members with the different staff categories (scientists, engineers and technicians, students) revealed a high degree of satisfaction of all members, with complete absence of dissenting voices. Even scientists who recently had to change subject, or students lacking publication, confirm being entirely satisfied by unit management.

The unit director has instaured a policy for identification and choice of scientific topics and projects. There are regular unit meetings, including journal clubs, meetings devoted to team projects, and meeetings devoted to general unit matters (twice yearly full-day).

Unit scientists are strongly involved in teaching veterinary students. Next to teaching of Molecular Physiology, they co-organize a master 2 program. Moreover, 6 PhD students and another 12 master 1 or master 2 students were trained betwen 2006 and 2010.

- **Appreciation on the project**

The unit proposes three main projects. Remarkably, none of these is identical to one of the five projects pursued in the previous period. Thus, the unit proposes a fairly radical scientific re-orientiation. All projects are clearly designed with a long-term perspective.

The first project follows on previous efforts to obtain tolerogenic DCs using heme-oxygenase and proposes to use ß2-adrenergic stimulation to this end. Preliminary data obtained in the OT-I system are shown suggesting that these reagents modify APC function and downregulate uptake, degradation and presentation of ovalbumin. ß2-stimulants do not protect NOD mice from diabetes, however chemical sympathectomy increases disease incidence. The project is structured in three parts and proposes a number of straightforward projects aiming to assess the effect of ß2 stimulation on antigen presentation to CD8+ cells and CD4+ cells in the ovalbumin model, and on autoimmunity in the NOD model and in patient PBMC. Experiments are fairly descriptive, and truly mechanistic studies are not proposed. Tools required for the project are available (pharmacological, surgical, electrical intervention). This project is risky as no strong preliminary evidence for protection from diabetes is available. It would seem advisable to start with NOD protection experiments since the project will be of less clinical interest if such an effect cannot be shown. There is also a concern as to the practical impact of the approach, as long-term ß2-stimulation would not be without side effects in the clinic.

The second project concerns micro-RNAs in type 1 diabetes. These miRNAs are known to have both immunostimulatory and gene silencing effects. A preliminary screening revealed that two miRNAs (503 and 877) were reduced in serum from NOD mice. On the other hand, miRNA 29b induced secretion of type I interferon from DCs in vitro and in vivo, and protected mice from diabetes upon transfer of CD8+ T cells recognizing beta cell-expressed hemagglutinin in a transgenic model. Thus, the underlying hypothesis here is that miRNAs might be of interest both as diagnostic and as therapeutic tools in diabetes. An ambitious program is proposed that aims to 1) determine a diabetes-associated miRNA fingerprint (both in the NOD model and in patients), 2) identify the cellular source of miRNAs with altered expression in T1D, 3) evaluate immunomodulatory effects of miRNAs. Here a particularly ambitious program is formulated that includes analyzing effects on APC subtypes by various methods, studying effects of miRNAs released by apoptotic cells, examining mice with a global deficiency of miRNAs (Dicer k.o.), and identify targets of miRNAs of interest. This project is potentially of high interest and certainly innovative, however it is associated with a number of risks that include strong competition in the field, technical challenges, possibly insufficient funding, and an overly ambitious wide-ranging program.

The third project is to be developped in collaboration with the IHU project team at the University of Nantes. Aim 1 concerns development of immuno-protected (encapsulated) pig islets. The strategy employed is apparently already being developped commercially by a New Zealand-based company, and it would have been good to spell out what specific aspects, competitive advantages or industry perspectives relative to that company are present in Nantes that justify this project. A second aim concerns development of the « European pig for medical use », a project under construction, as discussed above. Overall the third project seems to be in its planning stage as funding is not yet

available and staff is not clearly assigned. This project is evidently particularly consistent with the specific environment of a research unit at a veterinary school.

The unit has a policy for assigning staff to projects. Staff assigned to each of the two main projects is clearly identified (3.5 full-time equivalents for project 1, 3.2 for project 2).

All projects of the unit are fairly original and explore recent fields and therefore have the potential to be « cutting edge ».

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
IMMUNOENDOCRINOLOGIE CELLULAIRE ET MOLÉCULAIRE	B	B	A+	A	B

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	**42**	**5**	**20**	**26**	**36**	**59**	**5**	**17**	**29**	**239**
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

*** les résultats SVE2 ne sont pas définitifs au 06/05/2011.**

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

- **SVE1 Biologie, santé**
  - **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
  - **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
  - **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
  - **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
  - **SVE1_LS5 Neurosciences**
  - **SVE1_LS6 Immunologie, Infectiologie**
  - **SVE1_LS7 Recherche clinique, Santé publique**
- **SVE2 Ecologie, environnement**
  - **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
  - **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
  - **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

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Resp.: JM Bach

Nantes, April 18th, 2011

Comments on the AERES report of the CMIE Unit
Date of the visit by the AERES Review Committee: February 15, 2011.

We want first to thank the members of the AERES committee for their positive comments and constructive recommendations. We would like to address the following points made by the committee:

- Appreciation on the results: the AERES committee highlights main research events of the previous research period on type 1 diabetes:

- We agree that, out of five research projects, the study of the role of $CD8^+$ T cells in this disease proved "successful and allowed for publication of several articles (6) with good impact factor and citation rate". In this context, we began for few years the study of mechanisms regulating the $CD8^+$ T cell aggressive responses, in particular, the role of innate immunity receptors and microRNAs (miRNA) in the first phases of the aggression of pancreatic beta cells aiming to define new therapeutic targets and biomarkers of the disease complementary to $CD8^+$ T cells.
- The dendritic cell tolerization project (targeting either the HO-1 or the beta 2-AR pathways) was also productive with 2 articles published, 1 submitted and 1 in preparation for submission in June 2011. The HO-1 study will logically end in about 8-10 months because of the absence of evident scientific evolution as the role of this pathway on type 1 diabetes evolution in mouse models [transgenic and non obese diabetic (NOD)] as well as molecular mechanisms have been largely explored by us and others.
- The Myeloid-derived Suppressor Cell and the Insulin-secreting Stem Cell projects actually gave more limited scientific production (4 papers published) and we collectively decided to freeze these projects.
- The promising pet cancer project that has been incubated in our unit for the last four years will be developed by a new independent group (AMARoC) emerging from our Unit in 2012.

- Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners: the AERES committee appreciated our degree of local and national insertion. In complement, we are aware that developing international collaborations is of high priority to attract high-level scientists as well as high-amount funding. Increasingly widespread European collaborations are being developed (Belgium, Italy), especially in the context of the Nantes IHU project. We fully agree also that additional fund raising next to recurrent lump sum funding is pivotal for the development and scientific production of the proposed projects. Even if unit leaders were moderately successful in fund raising over the previous period (500 k€ by 7 researchers), we would like to draw your attention to the fact that half of this amount was obtained by the researchers that will lead the two principal projects in the future.

- The Nantes IHU project on an "European Center for Transplantation Sciences and Immunotherapy" was selected as a "promising" IHU and positively rated by the French National Agency for Research but, due to high competition, it was retained only for partial funding (15-20 million € including industrial contributions). Our project on xenotransplantation in type 1 diabetes [preclinical studies and development of an European Pig for Medical Use (PEPMU)] retains today all its priority. Following the evaluation visit, a regional grant has been requested for this program (Coordinator and PI: CMIE Unit, Letter of Intention accepted, > 1 million €, 9

partners including 1 industry and 2 European partners). Moreover, a R&D position has been obtained from the region to promote the PEPMU development.

- Since the evaluation visit, two other research grant proposals were submitted, one to a private organization (EFSD, 100 k€) in support of the beta 2-AR project, and a second one, based on our immunomonitoring platform, to the public FUI/Oseo for a collaborative R&D partnership with biotechs (Toulouse, Montpellier) and an INSERM unit (Toulouse) (>600 k€ for the CMIE Unit). Additional grant proposals with deadlines scheduled before the end of 2011 have been identified and applications are in preparation (especially for the miRNA project).
- Concerning scientist recruitments, we may mention that, since the evaluation, one postdoc was recruited on the DC tolerization project and, as mentioned during the interview and in our document, we plan to recruit in 2012 at least one more postdoc to develop the miRNA project. In the context of our xenotransplantation project in the IHU, we aim to recruit one postdoc and a research engineer with financial support from the above mentioned regional grant asked.

- **Appreciation on the strategy, management and life of the research unit**: the report mentions a positive appreciation on laboratory management and life of the research unit, and a high degree of satisfaction of all staff members, including for PhD students without accepted publications. We stress here the fact that all of PhD students (6) of the previous period obtained at least one publication in an international peer-reviewed journal. Similarly, both PhD students presently in our Unit will have a first author publication submitted in few months. More generally, we consider that good management and unit life is a prerequisite to scientific quality and enabled, in our case, the positive thematic refocusing.

- **Appreciation on the project**: the committee's report qualifies the proposed CMIE's research project as a « fairly radical re-orientation » in comparison to research carried out in the previous period. Constrained to a one-hour presentation to the AERES committee, we intentionally focused on innovative aspects of the proposed research, at the expense of ongoing projects, including the very productive project on autoreactive $CD8^+$ T-cells. Updated information on these projects was provided in an accompanying brochure distributed to all jury members in addition to the document submitted to the AERES in October 2010. In fact, the Lymphoscreen biocollection supporting the CD8 project is continuously growing (currently >100 samples, 2-5 samples included per month) and continues to be exploited for the identification and characterization of new autoreactive $CD8^+$ T-cell epitopes (one other paper will be submitted for publication in 2011). In continuity of this study, the ongoing beta 2-AR pathway and miRNA projects aim to effectively take advantage of the immunological and clinical data collected in order to study associations between (1) beta 2-AR polymorphism and type 1 diabetes and (2) the expression of specific miRNA as alternative markers of diabetes immune stages. A third project corresponding to our IHU implication completes these studies. The report further qualifies the proposed research « as potentially of high interest and certainly innovative », but is concerned about risks due to strong competition and technical challenges. We shall address this point separately for each research project:

- Project 1: Based on our preliminary data showing that beta 2-AR stimulation of dendritic cells leads to tolerogenic effects (Hervé J et al, beta 2-adrenergic stimulation of dendritic cells inhibits cross-presentation and mediates tolerance, expected submission in June 2011), we postulate that (i) beta 2-AR pathway dysfunction may account for self antigen tolerance breakdown leading to type 1 diabetes or (ii) beta 2-AR overstimulation may alternatively prevent tolerance breakdown. As recommended by the committee members, we will rapidly focus on the spontaneously diabetic NOD mouse model to check whether modulating beta 2-AR signalling might be of clinical interest, as suggested by preliminary data demonstrating that sympathectomy dramatically increases diabetes incidence in male NOD mice. Also, we agree that the proposed experiments in the autoimmune context were quite descriptive. Because of time limitation for presentation, we did not expose experiments using transgenic NOD mouse models such as the NOD 8.3 mouse (that exhibits a transgenic $CD8^+$ repertoire that specifically

recognizes an identified IGRP class I peptide) or the BDC2.5 mouse (that exhibits a transgenic $CD4^+$ repertoire that specifically recognizes an identified chromogranin A class II peptide) which shall help to study thoroughly the mechanisms involved in tolerance induction. Moreover, as mentioned by the committee members, numerous tools required for this project are available rendering it highly feasible and, from our point of view, less risky than suggested by the evaluation committee. The committee members seem to be concerned about side effects related to beta 2-AR long-term stimulation in diabetic patients; indeed, beta 2 agonists can induce a transient hyperglycaemia in patients that needs to be rigorously monitored in diabetic patients. However, it is also described that asthmatic diabetic young patients are efficiently treated using beta 2 agonists with ameliorated glycaemia control (Konig P et al, 2005; Wright NP and Wales JK, 2003). Furthermore, the clinical relevance of our project is not merely based on the use of beta 2 agonists to prevent type 1 diabetes onset, but also on the study of the integrity of the beta 2-adrenergic pathway in autoimmune patients, since the beta 2-AR gene is located in a susceptibility region for diabetes in the BB rat and for multiple sclerosis in humans. Putative beta 2-AR pathway dysfunction related to human type 1 diabetes, could pave the way for therapeutic restoration of this signalling pathway in dendritic cells.

- Project 2: We are aware of the fact that the first aim of project 2 - identification of miRNA biomarkers for diabetes - is a research field exposed to strong international competition. Our chance to succeed this aim is built on our existing widespread interactions with clinicians, the already existing and continuously growing human biocollection, and technical skills acquired in previous studies in mice. As presented to the evaluation committee, candidate miRNAs with differential expression in spontaneously diabetic NOD mice have been selected from whole miRNome serum profiles and entered a phase of validation on an enlarged panel of sera derived from mice at different stages of disease onset or progression. On the contrary, in aim 2 of this project, we focus on immunomodulatory effects of miRNAs by direct binding to receptors of innate immunity. This property needs to be distinguished from well-known effects of miRNAs on the immune response through RNA interference. To our knowledge, we are the first to explore this innovative hypothesis minimizing threats of international competition. A first manuscript on immunomodulatory beta cell miRNA and a second one on miRNA as diabetes makers in mouse are in preparation with submission in June 2011 and in July 2011, respectively.
- Project 3: We are convinced that the xenotransplantation project of the "promising" Nantes IHU takes place among the few groups which may be able to bring xenogeneic cells or tissues to the clinics within the next five years for several reasons: (i) twenty-year involvement of regional teams in xenotransplantation research (including our research Unit in the past) (ii) unique preclinical model plateforms (iii) network of international partnerships based on complementary specific skills ranging from fundamental to applied science aspects (iv) the presence of the Nantes Veterinary School ONIRIS and close partnerships with INRA and with two other leading European groups, UCL, Brussels and Padova, Italy, all institutions associated to producing a PEPMU, together with a highly committed and qualified industrial partner (Groupe Grimaud). This project will be developed together with the recruitment of dedicated staffs and funds already asked or obtained (R&D position) as mentioned above.

In **conclusion**, the ultimate goal of research management in our unit is to increase the number of researchers without teaching duties per project in a sustained effort to adapt to increasing international competition. Hopefully, publications of data obtained in our three projects will increase our international visibility and credibility, and our chances to succeed more effective fund raising in the near future.

(Jean-Marie BACH - For the CMIE Unit)

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